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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,151	01/31/2002	Patrick G. Hogan	10861-004002	3552

26161 7590 11/15/2004

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BOSTON, MA 02110

EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,151	HOGAN ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *145-165* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *154* is/are allowed.

6)☒ Claim(s) *145-152 and 156-165* is/are rejected.

7)☒ Claim(s) *153 and 155* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01312002 12292003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison A, B*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 145-164 in the reply filed on 08/23/2004 is acknowledged. The traversal is on the ground(s) that the polypeptides are species of SEQ ID NO: 77. This is found persuasive, and thus the Restriction Requirement is withdrawn. The polypeptides of SEQ ID NO: 5, 6, 7, 71, 77 will be examined. Claims 145-165 are pending and under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 145-152, 156-165 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for polypeptides consisting of, or comprising, SEQ ID NO: 5, 6, 7, 71, 77 wherein the peptide inhibits the protein-protein interaction between calcineurin and NFAT, does not reasonably provide enablement for polypeptides comprising SEQ ID NO: 5, 6, 7, 71, 77; for polypeptides 10-100 amino acids in length comprising SEQ ID NO: 5, 6, 7, 71, 77; or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to polypeptides comprising SEQ ID NO: 5, 6, 7, 71, 77; for polypeptides 10-100 amino acids in length comprising SEQ ID NO: 5, 6, 7, 71, 77; or variants thereof. Claims 145-152, 156-165 are overly broad since insufficient guidance is provided as to the function of these variant polypeptides. The claims are directed to variant polypeptides.

However, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins the claimed peptides. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, As an example of the unpredictable effects of mutations on protein function, Mickle et al. (Mickle JE et al. Genotype-phenotype relationships in cystic fibrosis. Med Clin North Am. 2000 May;84(3):597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (Voet et al. Biochemistry. 1990. John Wiley & Sons, Inc. pages 126-128 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino

acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a functional limitation for the variant polypeptides. Additionally, the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for

polypeptide variants, and has not taught how to make polypeptide variants, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

Claims 145-152, 156-165 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to polypeptides comprising SEQ ID NO: 5, 6, 7, 71, 77; for polypeptides 10-100 amino acids in length comprising SEQ ID NO: 5, 6, 7, 71, 77; or variants thereof. These are genus claims because the claims are thus directed to variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the

disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 5, 6, 7, 71, 77 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 145-146, 152, 156, 165 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,612,455 (Hoey).

The claims are drawn, *inter alia*, to polypeptides comprising SEQ ID NO: 5 and 77. The '455 patent discloses polypeptides of NFAT which comprise the sequences as set forth in SEQ ID NO: 5 and 77 (see Sequence Comparison A, attached), thus claims 145-146, 152, 165 are anticipated. The '455 patent further discloses fusion proteins comprising the NFAT peptides, thus claim 156 is anticipated.

Claims 145-151 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/26959 (Hoey).

The claims are drawn to, *inter alia*, polypeptides comprising SEQ ID NO: 6, 71, 77, and peptides less than 100, 50, 30, 20, 10 amino acids. The Hoey reference teaches polypeptides of NFAT which comprise the sequences as set forth in SEQ ID NO: 6, 71, 77 (see Sequence Comparison B, attached), thus claims 145-146 are anticipated. The Hoey reference further teaches fragments of NFAT proteins that are at least 5 amino acids, thus claims 147-151 are anticipated.

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Conclusion

Claim 154 is allowable.

Claims 145-152, 156-165 are rejected.

Claims 153, 155 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

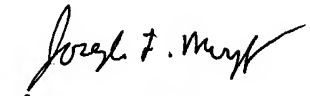
Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
October 28, 2004



JOSEPH MURPHY
PATENT EXAMINER

Sequence Comparison A

```
RESULT 8
US-08-396-479B-4
; Sequence 4, Application US/08396479B
; Patent No. 5612455
;  GENERAL INFORMATION:
;    APPLICANT:  HOEY, Timothy
;    TITLE OF INVENTION:  NUCLEAR FACTORS AND BINDING ASSAY
;    NUMBER OF SEQUENCES:  18
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  FLEHR, HOHBACH, TEST, ALBRITTON & HERBERT
;      STREET:  4 Embarcadero Center, Suite 3400
;      CITY:  San Francisco
;      STATE:  California
;      COUNTRY:  USA
;      ZIP:  94111
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/396,479B
;      FILING DATE:
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Osman, Richard A
;      REGISTRATION NUMBER:  36,627
;      REFERENCE/DOCKET NUMBER:  A-59450-1/RAO
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (415) 494-8700
;      TELEFAX:  (415) 494-8771
;      TELEX:  210 277299
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  716 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-396-479B-4

  Query Match             100.0%;  Score 30;  DB 1;  Length 716;
  Best Local Similarity   100.0%;  Pred. No. 62;
  Matches    6;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 PRIEIT 6
              ||||||
Db        118 PRIEIT 123
```

Sequence Comparison B

```
RESULT 8
AAW02250
ID   AAW02250 standard; protein; 902 AA.
XX
AC   AAW02250;
XX
DT   17-NOV-1996  (first entry)
XX
DE   Human transcription factor NFAT3.
XX
KW   Nuclear factor of activated T-cells; NFAT; NFAT3; transcription factor;
KW   cytokine; gene expression; binding assay; immune system disease; therapy;
KW   diagnosis.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   Domain          397. .686
FT                   /label= Rel_domain
XX
PN   WO9626959-A1.
XX
PD   06-SEP-1996.
XX
PF   04-MAR-1996;   96WO-US003113.
XX
PR   02-MAR-1995;   95US-00396479.
XX
PA   (TULA-) TULARIK INC.
XX
PI   Hoey T;
XX
DR   WPI; 1996-412738/41.
DR   N-PSDB; AAT36868.
XX
PT   DNA mol. encoding human nuclear factors of activated T cells - useful for
PT   screening potential therapeutic and diagnostic agents for immune system
PT   diseases.
XX
PS   Claim 5; Page 43-47; 64pp; English.
XX
CC   The amino acid sequence (AAW02250) of human nuclear factor of activated T
CC   -cells class 3, NAFT3, was deduced from an isolated cDNA clone
CC   (AAT36868). NFATs (see also AAW02248-49 and AAW02251-53) include
CC   regulators of cytokine gene expression that modulate immune system
CC   function. They have invariant rel domain peptides (see also AAW02254-55)
CC   and share at least 50% sequence identity in their rel domains.
CC   Recombinant NFATs, or NFAT fragments contg. at least part of the rel
CC   domain, can be expressed in prokaryotic or eukaryotic host cells. They
CC   are used in high-throughput screenings to identify agents useful in the
CC   diagnosis or treatment of diseases associated with expression of a gene
CC   modulated by a transcription complex contg. NFAT(s)
XX
SQ   Sequence 902 AA;

  Query Match             100.0%;  Score 29;  DB 2;  Length 902;
  Best Local Similarity   100.0%;  Pred. No. 6.4e+02;
  Matches    6;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 PSIRIT 6
              ||||||
Db        114 PSIRIT 119
```